Exhibit 2

Patents

Improved method for preparing tetrazole for valsartan

Abstract

The invention provides an improved method for preparing tetrazole from valsartan. The method comprises the following steps: (1) carrying out a thermal reaction between a compound I and valeryl chloride in an organic solvent in the presence of an acid-binding agent, thereby obtaining an oily compound II; (2) dissolving the compound II obtained in the step (1) in a strongly polar aprotic solvent, adding a certain amount of sodium azide and zinc chloride anhydrous, and reacting in the presence of a catalyst to obtain a solution of a compound III. The method is simple and convenient to operate, and has the advantages that the reaction conditions are relatively mild, the production cost is relatively low, impurities can be better controlled, and the requirement of later valsartan production for a high-quality intermediate can be met.

Classifications

- C07D257/04 Five-membered rings

CN104045602A
China

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Other languages: Chinese

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Claims (12)

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1. improving one's methods of a valsartan intermediate compound III, is characterized in that comprising the following steps:

(1), under the condition that Compound I exists at acid binding agent, in organic solvent, obtain oily matter Compound I I with n-amyl chloride insulation reaction;

(2) the Compound I I upper step being made is dissolved in the middle of strong polar aprotic solvent, adds a certain amount of sodium azide and Zinc Chloride Anhydrous, under the condition existing, obtains compound III solution at catalyzer; R=CH wherein $_3$, C $_2$h $_5$or

2. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that the middle acid binding agent of step (1) is one or both in sodium carbonate, salt of wormwood, sodium hydroxide, potassium hydroxide.

3. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (1), organic solvent is toluene, dimethylbenzene, methylene dichloride, is preferably toluene.

4. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (1), holding temperature is 15 ~ 35 ℃, preferably 20 ~ 25 ℃.

5. a kind of valsartan intermediate compound III according to claim 1 improves one's methods, it is characterized in that in step (2) that strong polar aprotic solvent is a kind of in DMF, N,N-dimethylacetamide, dimethyl sulfoxide (DMSO), be preferably DMF.

6. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that strong polar aprotic solvent quality consumption in step (2) is 2 ~ 3 times of Compound I I quality.

7. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that the middle sodium azide of step (2) and Compound I I mol ratio are 1.5: 1 ~ 2: 1.

8. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (2), Zinc Chloride Anhydrous quality consumption equates with sodium azide quality consumption.

9. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (2), catalyzer is that quaternary ammonium salt is selected from: methyl tricapryl ammonium chloride, benzyltriethylammoinium chloride, 4-butyl ammonium hydrogen sulfate; Or for metal halide is selected from lithium chloride, aluminum chloride, lithiumbromide, aluminum bromide, be preferably methyl tricapryl ammonium chloride, 4-butyl ammonium hydrogen sulfate, lithium chloride.

10. improving one's methods of a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (2), catalyst quality consumption is 2% ~ 10% of Compound I I quality.

Improving one's methods of 11. a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (2), becoming tetrazole temperature of reaction is 80 ~ 135 ℃, is preferably 80 ~ 100 ℃.

Improving one's methods of 12. a kind of valsartan intermediate compound III according to claim 1, is characterized in that in step (2), becoming the tetrazole reaction times is 8 ~ 35 hours, is preferably 8 ~ 15 hours.

Description

A kind of valsartan becomes improving one's methods of tetrazole

Technical field

The present invention relates to a kind of valsartan and become improving one's methods of tetrazole.

Background of invention

Its chemistry (S)-N-pentanoyl-N-[[2 '-(1H-5-tetrazole-yl) [1,1 '-biphenyl] by name-4 bases of valsartan] methyl] α-amino-isovaleric acid, structural formula is as follows:

Valsartan is developed by Switzerland Novartis company, is the cookle that Novartis casts in antihyperalgesic thing field, and valsartan expires in the patent of the U.S. at present, and valsartan imitation medicine has welcome one and taken turns peak, and preparation constantly amplifies the demand of API.Report document patent about valsartan has much at present, much tens of the report of relevant valsartan synthetic route, wherein according to becoming the mode difference of tetrazole to be mainly divided into two classes:

First kind route is with 2 '-cyano group-4-bromomethylbiphenyl and the synthetic tetrazole ring of nitrine root salt, for example take Valine as starting material is through esterification, carry out condensation reaction with 2 '-cyano group-4-bromomethylbiphenyl again, again through valeryl, become tetrazole to generate valsartan, and wherein become tetrazole step, it is the committed step of valsartan synthetic route, have bibliographical information with tributyl azide tin for becoming tetrazole critical component (WO2009125416, US20090203921), separately have bibliographical information with the metal-salt of hydrazoic acid for becoming tetrazole critical component, specifically with (S)-N-pentanoyl-N-[[2 '-cyano group-1, 1 '-biphenyl]-4 bases] methyl] figured silk fabrics ammonia ester, sodium azide, metal halide, about 130 ℃ reactions, within 30 hours, become tetrazole (CN101270096).The former has used hypertoxic metallic tin, causes residual being difficult to of aftertreatment tin to be controlled.Latter reaction's time is partially long, and transformation efficiency is not high, and temperature of reaction is higher, the more difficult control of impurity.

Equations of The Second Kind route be with 2 '-(N '-trityl) tetrazole base-4-bromomethylbiphenyl (BBTT) is through Deprotection, forms tetrazole ring.Specifically comprise that L-valine amide is raw material; through condensation, valeryl, Deprotection, generate valsartan; this route has been evaded one-tenth tetrazole ring severe condition used; it is more complicated that but this route operates relative route one; and condensation step is used expensive BBTT; deprotection operation also will be used expensive Pd/C, and (EP1849777, CN101045712) increased production cost.

The present invention mainly improves route 14 nitrogen azoles operation, with 2 '-cyano group-4-bromomethylbiphenyl, sodium azide and metal halide for becoming tetrazole critical component, for the shortcoming existing in bibliographical information (transformation efficiency is not high, long reaction time, temperature of reaction are high, the more difficult control of impurity).By selecting specific reaction solvent, add specific catalyzer, to becoming tetrazole condition to be optimized.

Summary of the invention

The object of the invention is to improve synthesizing Xieshatan method, the technique after improvement is applicable to suitability for industrialized production, and temperature of reaction is low, energy-saving safe, and the reaction times is short, has improved production capacity, and impurity is easy to control, good product quality.

More specifically, the invention provides improving one's methods of a kind of valsartan intermediate compound III, comprise the following steps:

(1), under the condition that Compound I exists at acid binding agent, in organic solvent, obtain oily matter Compound I I with n-amyl chloride insulation reaction;

(2) the Compound I I upper step being made is dissolved in the middle of strong polar aprotic solvent, adds a certain amount of sodium azide and Zinc Chloride Anhydrous, under the condition existing, obtains compound III solution at catalyzer.Described R is-CH_3,-C_2h_5or

The described acid binding agent of step (1) is one or both in sodium carbonate, salt of wormwood, sodium hydroxide, potassium hydroxide.

The described acid binding agent of step (1) and Compound I mol ratio are 2: 1 ~ 3: 1.

The described organic solvent of step (1) is toluene, dimethylbenzene, methylene dichloride, is preferably toluene.

The described holding temperature of step (1) is 20 ~ 30 ℃.

Step 2) detailed process, for the Compound I I that upper step is made is dissolved in the middle of strong polar aprotic solvent, adds a certain amount of sodium azide and Zinc Chloride Anhydrous, stirs, then adds catalyzer, and reacting by heating for some time, pilot process is controlled.After reaction finishes, feed liquid is cooled to room temperature.Add extraction solvent, water, quencher to carry out cancellation, acid adjustment, layering, washing, obtain compound III solution.

The described strong polar aprotic solvent of step (2) is a kind of in DMF (DMF), DMA (N,N-dimethylacetamide), DMSO (dimethyl sulfoxide (DMSO)).Be preferably DMF.

The described strong polar aprotic solvent quality consumption of step (2) is 2 ~ 3 times of Compound I I quality.

The described sodium azide of step (2) and Compound I I mol ratio 1.5: 1 ~ 2: 1.

The described Zinc Chloride Anhydrous consumption of step (2) equates with sodium azide quality consumption.

The described catalyzer of step (2) is that quaternary ammonium salt comprises: methyl tricapryl ammonium chloride, benzyltriethylammoinium chloride, 4-butyl ammonium hydrogen sulfate; Or for metal halide comprises lithium chloride, aluminum chloride, lithiumbromide, aluminum bromide, be preferably methyl tricapryl ammonium chloride, 4-butyl ammonium hydrogen sulfate, lithium chloride.

The described catalyst levels of step (2) is 2% ~ 10% of Compound I I quality.

The described one-tenth tetrazole of step (2) temperature of reaction is 80 ~ 135 ℃, is preferably 80 ~ 100 ℃.

The described one-tenth tetrazole reaction times of step (2) is 8 ~ 35 hours, is preferably 8 ~ 15 hours.

The described extraction solvent of step (2) is methyl tertiary butyl ether, diisopropyl ether, methyl phenoxide, toluene, is preferably methyl tertiary butyl ether.

The described quencher of step (2) is Sodium Nitrite, clorox.

The invention provides synthetic method easy and simple to handle, use catalyzer energy Reaction time shorten, reduce temperature of reaction, be conducive to production capacity and promote and Control of Impurities.Increase cancellation step after upper tetrazole operation completes, is conducive to reduce production danger coefficient, reduces the Health hazard to employee.

Embodiment

Following examples are specifically addressed the technology of the present invention, but content of the present invention is not limited to this:

Embodiment 1: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml toluene, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir molten clearly, be cooled to 20 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 98.0%, purity (HPLC): 99.2%, single assorted (HPLC): 0.11%, total assorted (HPLC): 0.7%.

Embodiment 2: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-C_2h_5) and 100ml toluene, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir molten clearly, be cooled to 20 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 97.5%, purity (HPLC): 98.9%, single assorted (HPLC): 0.15%, total assorted (HPLC): 1.0%.

Embodiment 3: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I with 100ml toluene, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir molten clearly, be cooled to 20 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 97.0%, purity (HPLC): 98.4%, single assorted (HPLC): 0.16%, total assorted (HPLC): 1.5%.

Embodiment 4: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml toluene, add 23.1g salt of wormwood (with Compound I I mol ratio be 2: 1) and 60ml water stir molten clearly, be cooled to 20 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 120ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 98.4%, purity (HPLC): 99.6%, single assorted (HPLC): 0.08%, total assorted (HPLC): 0.3%.

Embodiment 5: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml toluene, add 26.6g sodium carbonate (with Compound I I mol ratio be 3: 1) and 80ml water stir molten clearly, be cooled to 20 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 98.0%, purity (HPLC): 99.4%, single assorted (HPLC): 0.10%, total assorted (HPLC): 0.5%.

Embodiment 6: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml toluene, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir, be cooled to 30 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwise, insulated and stirred 2 hours, pilot process is controlled.Reaction finishes, branch vibration layer, and 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 98.4%, purity (HPLC): 99.5%, single assorted (HPLC): 0.11%, total assorted (HPLC): 0.5%.

Embodiment 7: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml dimethylbenzene, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir, be cooled to 30 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwises insulated and stirred 2 hours, pilot process is controlled, unreacted is complete, continues stirring reaction 2 hours, and reaction finishes, branch vibration layer, 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 98.2%, purity (HPLC): 98.5%, single assorted (HPLC): 0.18%, total assorted (HPLC): 1.4%.

Embodiment 8: the preparation of Compound I I

In 500ml four-hole bottle, add 30g Compound I (R=-CH_3) and 100ml methylene dichloride, add 17.7g sodium carbonate (with Compound I I mol ratio be 2: 1) and 80ml water stir, be cooled to 30 ℃, insulation drips 12g n-amyl chloride and 40ml toluene mixture liquid, dropwises insulated and stirred 2 hours, pilot process is controlled, unreacted is complete, continues stirring reaction 4 hours, and reaction finishes, branch vibration layer, 160ml water washing organic phase, solvent evaporated, obtains Compound I I, yield: 95.4%, purity (HPLC): 98.0%, single assorted (HPLC): 0.18%, total assorted (HPLC): 1.9%.

Embodiment 9: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 13 hours, compound III purity (HPLC): 98.1%, Compound I I residual (HPLC): 1.6%, single assorted (HPLC): 0.11%.

Embodiment 10: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 99gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds

and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 15 hours, compound III purity (HPLC): 97.5%, Compound I I residual (HPLC): 2.3%, single assorted (HPLC): 0.10%.

Embodiment 11: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMA of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 14 hours, compound III purity (HPLC): 98.0%, Compound I I residual (HPLC): 1.6%, single assorted (HPLC): 0.11%.

Embodiment 12: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMSO of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 11 hours, compound III purity (HPLC): 98.3%, Compound I I residual (HPLC): 1.4%, single assorted (HPLC): 0.10%.

Embodiment 13: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 10.6g sodium azide and 10.6g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 12 hours, compound III purity (HPLC): 98.9%, Compound I I residual (HPLC): 1.0%, single assorted (HPLC): 0.07%.

Embodiment 14: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 2 preparations, add 10.6g sodium azide and 10.6g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 12 hours, compound III purity (HPLC): 98.8%, Compound I I residual (HPLC): 1.1%, single assorted (HPLC): 0.07%.

Embodiment 15: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 3 preparations, add 10.6g sodium azide and 10.6g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 12 hours, compound III purity (HPLC): 98.5%, Compound I I residual (HPLC): 1.3%, single assorted (HPLC): 0.08%.

Embodiment 16: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 3.3g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 9 hours, compound III purity (HPLC): 98.3%, Compound I I residual (HPLC): 1.5%, single assorted (HPLC): 0.09%.

Embodiment 17: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g 4-butyl ammonium hydrogen sulfate, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 14 hours, compound III purity (HPLC): 97.8%, Compound I I residual (HPLC): 1.8%, single assorted (HPLC): 0.10%.

Embodiment 18: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g lithium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 12 hours, compound III purity (HPLC): 97.5%, Compound I I residual (HPLC): 1.8%, single assorted (HPLC): 0.12%.

Embodiment 19: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 100 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 10 hours, compound III purity (HPLC): 98.6%, Compound I I residual (HPLC): 1.2%, single assorted (HPLC): 0.12%.

Embodiment 20: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 120 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 9 hours, compound III purity (HPLC): 98.4%, Compound I I residual (HPLC): 0.7%, single assorted (HPLC): 0.15%.

Embodiment 21: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 135 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 8 hours, compound III purity (HPLC): 97.8%, Compound I I residual (HPLC): 0.6%, single assorted (HPLC): 0.19%.

Embodiment 22: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent diisopropyl ether, water and the cancellation of 8g Sodium Nitrite, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 13 hours, compound III purity (HPLC): 98.0%, Compound I I residual (HPLC): 1.5%, single assorted (HPLC): 0.11%.

Embodiment 23: the preparation of compound III

In 500ml four-hole bottle, add by Compound I I (about 33g) and the 66gDMF of example 1 preparation, add 8g sodium azide and 8g Zinc Chloride Anhydrous, stir, add 0.66g methyl tricapryl ammonium chloride, be warming up to 80 ℃, stirring reaction, pilot process is controlled.Reaction finishes, and is down to room temperature, adds and extracts solvent methyl tertiary butyl ether, water and the cancellation of 8.6g clorox, acid adjustment.Branch vibration layer, washing organic phase, obtain compound III solution.Reaction times: 13 hours, compound III purity (HPLC): 98.0%, Compound I I residual (HPLC): 1.6%, single assorted (HPLC): 0.12%.

Embodiment 24: the preparation of valsartan

In 500ml four-hole bottle, add by the compound III solution of example 13 preparations, be cooled to-5 ~ 15 ℃, be incubated and drip alkali lye, alkaline hydrolysis 8 ~ 15 hours, pilot process is controlled, and alkaline hydrolysis reaction finishes, and divides and goes upper organic phase, and water is refunded reaction flask.Add ethyl acetate, reaction solution is cooled to-5 ~ 10 ℃, insulation acid adjustment, and acid adjustment finishes, minute sub-cloud water.Organic phase washes twice with water, dry, concentrated.To concentrated solution, add a certain amount of ethyl acetate, cooling crystallization, filtration, oven dry.Obtain valsartan, purity (HPLC): 99.88%, always assorted: 0.11, single assorted (HPLC): 0.05%.

Patent Citations (3)

Publication number	Priority date	Publication date	Assignee	Title
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CN102010381A *	2009-09-05	2011-04-13	山东新时代药业有限公司	Improved preparation method of valsartan
CN102822151A *	2010-04-07	2012-12-12	新梅斯托克公司	Improved process for preparing valsartan
Family To Family Citations				

* Cited by examiner, † Cited by third party

Cited By (3)

Publication number	Priority date	Publication date	Assignee	Title
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WO2020010643A1 *	2018-07-13	2020-01-16	浙江华海药业股份有限公司	Method for synthesizing valsartan
CN111072581A *	2018-10-22	2020-04-28	珠海润都制药股份有限公司	Valsartan free of genotoxic impurities and preparation method thereof
Family To Family Citations				

* Cited by examiner, † Cited by third party, ‡ Family to family citation

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CN101704788B	2011-09-07	Improved preparation process of 2-Butyl-1,3-diazapira[4,4]nonane-1-en-4-one
CN103833530A	2014-06-04	Preparation method of organic intermediate 3-phenoxyl-1, 2-propylene glycol
CN102093257B	2013-09-11	Method for preparing 2,2-diisopropylpropionitrile
CN104356155B	2017-01-18	Preparation method of (S)-tert-butyldimethylsilyloxy-glutaramate
CN101602760A	2009-12-16	A kind of preparation method of olmesartan medoxomill
CN107573345A	2018-01-12	A kind of Ai Dailalisi and its intermediate preparation method
CN103613531B	2015-06-17	Synthesis method of 1-tert-butylmethoxycarbonyl-3-piperidone
CN102962004B	2015-04-15	Glucosamide surfactant and method for preparing same
US11512044B2	2022-11-29	Method for preparing salicylamine acetate
CN105924400A	2016-09-07	Preparation method for azilsartan impurity A and azilsartan impurity B
CN102633753B	2014-05-28	Method for synthesizing carbobenzoxyserine-beta-lactone

Priority And Related Applications

Priority Applications (1)

Application	Priority date	Filing date	Title
CN201410307545.7A	2014-06-28	2014-06-28	Improved method for preparing tetrazole for valsartan

Applications Claiming Priority (1)

Application	Filing date	Title
CN201410307545.7A	2014-06-28	Improved method for preparing tetrazole for valsartan

Legal Events

Date	Code	Title	Description
2014-09-17	C06	Publication	
2014-09-17	PB01	Publication	
2017-06-20	SE01	Entry into force of request for substantive examination	
2017-06-20	SE01	Entry into force of request for substantive examination	
2019-12-27	RJ01	Rejection of invention patent application after publication	**Application publication date**: 20140917
2019-12-27	RJ01	Rejection of invention patent application after publication	

Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
C09CA03 - Valsartan		title,claims,abstract,description	29	0.000
valsartan		title,claims,abstract,description	29	0.000
valsartan		title,claims,abstract,description	29	0.000
tetrazoles		title,claims,abstract,description	21	0.000
compounds		claims,abstract,description	142	0.000
chemical reaction		claims,abstract,description	54	0.000

sodium azide	claims,abstract,description	50	0.000
acid	claims,abstract,description	24	0.000
polar aprotic solvent	claims,abstract,description	8	0.000
binding agent	claims,abstract,description	6	0.000
organic solvent	claims,abstract,description	5	0.000
sodium;zinc;trichloride	claims,abstract,description	4	0.000
catalyst	claims,abstract,description	3	0.000
toluene	claims,description	37	0.000
reaction time	claims,description	21	0.000
methyl group	claims,description	19	0.000
sodium carbonate	claims,description	18	0.000
Ammonium chloride	claims,description	17	0.000
Zinc chloride	claims,description	17	0.000
ammonium chloride	claims,description	17	0.000
monochloramine	claims,description	17	0.000
zinc chloride	claims,description	17	0.000
zinc chloride	claims,description	17	0.000
insulation	claims,description	11	0.000
1-Chloropentane	claims,description	10	0.000
Lithium chloride	claims,description	10	0.000
sodium carbonate	claims,description	9	0.000
sodium carbonate	claims,description	9	0.000
sodium hydroxide	claims,description	8	0.000
potassium hydroxide	claims,description	6	0.000
N,N-dimethylformamide	claims,description	5	0.000
butan-1-amine;sulfuric acid	claims,description	5	0.000
dimethylsulphoxide	claims,description	5	0.000
Aluminium chloride	claims,description	4	0.000
Lithium bromide	claims,description	4	0.000
metal halide	claims,description	4	0.000
metal halides	claims,description	4	0.000
DMA	claims,description	3	0.000
methylene dichloride	claims,description	3	0.000
o-xylene	claims,description	3	0.000
potassium carbonate	claims,description	3	0.000
potassium carbonate	claims,description	3	0.000
Aluminium bromide	claims,description	2	0.000
chloride anion	claims,description	2	0.000
lithium bromide	claims,description	2	0.000
quaternary ammonium salts	claims,description	2	0.000

tolyl group	claims	1	0.000
manufacturing process	abstract,description	7	0.000
impurity	abstract,description	5	0.000
pentanoyl chloride	abstract	1	0.000

Show all concepts from the description section